

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Intrinsa 300 micrograms/24 hours transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch of 28 cm² contains 8.4 mg testosterone and provides 300 micrograms of testosterone per 24 hours.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch.

Thin, clear, oval matrix-type transdermal patch consisting of three layers: a translucent backing film, an adhesive matrix drug layer, and a protective release liner that is removed prior to application. Each patch surface is stamped with PG T001.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intrinsa is indicated for the treatment of hypoactive sexual desire disorder (HSDD) in bilaterally oophorectomised and hysterectomised (surgically induced menopause) women receiving concomitant estrogen therapy.

4.2 Posology and method of administration

The recommended daily dose of testosterone is 300 micrograms. This is achieved by applying the patch twice weekly on a continuous basis. The patch should be replaced with a fresh patch every 3 to 4 days. A particular application site should be rotated with an interval of at least 7 days between applications. Only one patch is to be worn at a time.

The adhesive side of the patch should be applied to a clean, dry area of skin on the lower abdomen below the waist. Patches should not be applied to the breasts or other body regions. A skin site with minimal wrinkling and not covered by tight clothing is recommended. The site should not be oily, damaged, or irritated. To prevent interference with the adhesive properties of Intrinsa, no creams, lotions or powder should be applied to the skin where the patch is to be applied.

The patch should be applied immediately after opening the sachet and removing both parts of the protective release liner. The patch should be pressed firmly in place for about 10 seconds, making sure there is good contact with the skin, especially around the edges. If an area of the patch lifts, pressure should be applied to that area. If the patch detaches prematurely, it may be reapplied. If the same patch cannot be reapplied, a new patch should be applied to another location. In either case, the original treatment regimen should be maintained. The patch is designed to remain in place during a shower, bath, swimming or exercising.

Concomitant estrogen treatment

The appropriate use and restrictions associated with estrogen therapy should be considered before Intrinsa therapy is initiated and during routine re-evaluation of treatment. Continued use of Intrinsa is only recommended while concomitant use of estrogen is considered appropriate (i.e. the lowest effective dose for the shortest possible duration).

Patients treated with conjugated equine estrogen (CEE) are not recommended to use Intrinsa, as efficacy has not been demonstrated (see sections 4.4 and 5.1).

Duration of treatment

Intrinsa treatment response should be evaluated within 3-6 months of initiation, to determine if continued therapy is appropriate. Patients who do not experience a meaningful benefit should be re-evaluated and discontinuation of therapy be considered.

As the efficacy and safety of Intrinsa have not been evaluated in studies of longer duration than 1 year, it is recommended that an appraisal of the treatment is undertaken every 6 months.

Children and adolescents:

There is no relevant indication for use of Intrinsa in children and adolescents.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Known, suspected or past history of cancer of the breast or known or suspected estrogen-dependent neoplasia, or any other condition consistent with the contraindications for the use of estrogen.

4.4 Special warnings and precautions for use

At regular intervals during treatment, physicians should monitor patients for potential androgenic undesirable effects (e.g. acne, changes in hair growth or hair loss). Patients should be advised to self assess for androgenic undesirable effects. Signs of virilisation, such as voice deepening, hirsutism or clitoromegaly, may be irreversible and discontinuation of treatment should be considered. In clinical trials these reactions were reversible in the majority of patients (see section 4.8).

Severe skin erythema, local oedema and blistering may occur due to hypersensitivity to the patch at the site of application. Use of the patch should be discontinued if this occurs.

The safety of Intrinsa has not been evaluated in double blind placebo controlled studies of longer than 1 year duration. There is little information on long-term safety, including effects on breast tissue, the cardiovascular system and increase in insulin resistance.

Data in the literature regarding the influence of testosterone on the risk of breast cancer in women are limited, inconclusive and conflicting. The long-term effect of testosterone treatment on the breast is currently unknown, therefore patients should be carefully monitored with regard to breast cancer in accordance with currently accepted screening practises and individual patient needs.

Patients with known cardiovascular disease have not been studied. Patients with cardiovascular risk factors, in particular hypertension, and patients with known cardiovascular disease should be carefully monitored, specifically regarding changes in blood pressure and weight.

In diabetic patients the metabolic effects of testosterone may decrease blood glucose and therefore insulin requirements. Patients with diabetes mellitus have not been studied.

Little information is available on the effects of testosterone on the endometrium. The limited data evaluating the effect of testosterone on the endometrium neither allow conclusions nor reassurances on the incidence of endometrial cancer.

Oedema (with or without congestive heart failure) may be a serious complication from high doses of testosterone or other anabolic steroids in patients with pre-existing cardiac, renal, or hepatic disease. However, this is not expected from the low dose of testosterone delivered by the Intrinsa patch.

Intrinsa is recommended for use in surgically menopausal women up to the age of 60. Consistent with the prevalence of HSDD, there are limited data above the age of 60.

Efficacy and safety of Intrinsa 300 micrograms in naturally menopausal women with HSDD on concomitant estrogen, with or without progestogen, have not been evaluated. Intrinsa 300 micrograms is not recommended in naturally menopausal women.

Whereas Intrinsa is indicated with concomitant estrogen therapy, the subgroup of patients receiving oral conjugated equine estrogens (CEE) did not demonstrate a significant improvement in sexual function. Therefore, Intrinsa should not be used in women on concomitant CEE (see sections 4.2 and 5.1).

Androgens may decrease levels of thyroxin-binding globulin, resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. When testosterone is given concomitantly with anticoagulants, the anticoagulant effect may increase. Patients receiving oral anticoagulants require close monitoring, especially when testosterone therapy is started or stopped.

4.6 Pregnancy and lactation

Intrinsa must not be used in women who are or may become pregnant or by breast-feeding women.

Testosterone may induce virilising effects on the female foetus when administered to a pregnant woman. Studies in animals have shown reproductive toxicity (see section 5.3).

In case of inadvertent exposure during pregnancy, use of Intrinsa must be discontinued.

4.7 Effects on ability to drive and use machines

Intrinsa has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The adverse reaction most often reported (very common $\geq 1/10$), was application site reactions (30.4 %). The majority of these adverse reactions consisted of mild erythema and itching and did not result in patient withdrawal. No very common adverse reactions were reported at a greater incidence in the Intrinsa group than the placebo group.

During 6-month double blind exposure the following adverse reactions occurred in the treatment group (n=549) at a greater incidence than placebo (n=545) and were assessed by the investigators as possibly or probably related to Intrinsa treatment.

MedDRA System organ class	Common $\geq 1/100, < 1/10$	Uncommon $\geq 1/1,000, < 1/100$
Infections and infestations		Sinusitis
Blood and lymphatic system disorders		Abnormal clotting factor
Immune system disorders		Hypersensitivity
Metabolism and nutrition disorders		Increased appetite
Psychiatric disorders	Insomnia	Agitation, anxiety
Nervous system disorders	Migraine	Disturbance in attention, dysgeusia, impaired balance, hyperaesthesia, oral paraesthesia, transient ischemic attack

MedDRA System organ class	Common ≥ 1/100, < 1/10	Uncommon ≥ 1/1,000, < 1/100
Eye disorders		Diplopia, eye redness
Cardiac disorders		Palpitations
Respiratory, thoracic and mediastinal disorders	Voice deepening	Nasal congestion, throat tightness
Gastrointestinal disorders		Diarrhoea, dry mouth, nausea
Skin and subcutaneous tissue disorders	Acnes, alopecias, hirsutism	Eczema, increased sweating, rosacea
Musculoskeletal and connective tissue disorders		Arthritis
Reproductive system and breast disorders	Breast pain	Breast cyst, clitoral engorgement, enlarged clitoris, genital pruritus, vaginal burning sensation
General disorders and administration site conditions		Anasarca, asthenia, chest tightness, chest discomfort
Investigations	Increased weight	Abnormal blood fibrinogen, increased heart rate, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin, abnormal liver function test, increased blood triglycerides

Ninety-one to 96 % of reports of acne, hirsutism, voice deepening and alopecia were considered mild. These reactions were reversible in the majority of patients who dropped out due to them. Nine patients in the Intrinsa group (1.6 %) and 3 patients in the placebo group (0.6 %) withdrew from the study because of these reactions. All other common adverse events resolved in the majority of patients.

4.9 Overdose

The mode of administration of Intrinsa makes overdose unlikely. Removal of the patch results in a rapid decrease in serum testosterone levels (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Androgens, testosterone, ATC code: G03BA03

Testosterone, the primary circulating androgen in women, is a naturally occurring steroid, secreted by the ovaries and adrenal glands. In premenopausal women, the rate of production of testosterone is 100 to 400 micrograms/24 hours, of which half is contributed by the ovary as either testosterone or a precursor. Serum levels of androgens fall as women age. In women, who have undergone bilateral oophorectomy, serum levels of testosterone decline by approximately 50 % within days after surgery.

Intrinsa is a transdermal therapy for HSDD, which improves sexual desire while achieving testosterone concentrations compatible with premenopausal levels.

Two multi-centre, double-blind, placebo-controlled six month studies in 562 (INTIMATE SM1) and 533 (INTIMATE SM2) oophorectomised and hysterectomised women (surgically induced menopause), aged 20 to 70 years, with HSDD on concomitant estrogen were used to evaluate the efficacy and safety of Intrinsa. Total satisfying sexual activity (primary endpoint), sexual desire, and

distress associated with low sexual desire (secondary endpoints) were evaluated with validated instruments.

In the combined study analysis at 24 weeks, the difference in the mean frequency of total satisfying episodes between Intrinsa and placebo was 1.07 per 4 weeks.

A significantly higher percentage of women who received Intrinsa reported a benefit in the three endpoints, that they considered clinically meaningful compared to women who received placebo. In the combined phase III data, excluding patients taking oral CEE, in whom there was no significant improvement in sexual function, 50.7 % of women (n=274) treated with Intrinsa and 29.4 % of those treated with placebo (n=269) were responders with regard to total satisfying sexual activity (primary endpoint), when a responder was predefined as having an increase in the 4-week frequency of satisfying activities of > 1.

Effects of Intrinsa were observed at 4 weeks after initiation of therapy (the first measured time point) and at all monthly efficacy time points thereafter.

Efficacy versus placebo was significant across a range of subgroups which included patients separated by the following baseline characteristics: age (all subgroups up to age 65 years); body weight (up to 80 kg) and oophorectomy (up to 15 years ago).

Subgroup analyses suggested that the route and type of concomitant estrogen (transdermal oestradiol, oral conjugated equine estrogen (CEE), oral non-CEE) can influence patient response. A responder analysis of the pivotal phase II and III studies showed significant improvements in all three major clinical endpoints versus placebo in patients on concomitant transdermal and oral non-CEE estrogens. However, the subgroup of patients receiving oral CEE did not demonstrate a significant improvement in sexual activity compared to placebo (see sections 4.2 and 4.4).

5.2 Pharmacokinetic properties

Absorption:

Testosterone from Intrinsa is transported across intact skin by a passive diffusion process that is primarily controlled by permeation across the stratum corneum. Intrinsa is designed to systemically deliver 300 micrograms/day. Following application of the patch on abdominal skin, maximum serum concentrations of testosterone are reached within 24-36 hours, with a wide inter-individual variability. Serum concentrations of testosterone attain steady-state by the application of the second patch when applied in a twice-a-week regimen. Intrinsa did not influence serum concentrations of sex hormone binding globulin (SHBG), estrogens or adrenal hormones.

Hormone	Baseline		Week 24		Week 52	
	N	Mean (SEM)	N	Mean (SEM)	N	Mean (SEM)
Free testosterone (pg/ml)	544	0.92 (0.03)	412	4.36 (0.16)	287	4.44 (0.31)
Total testosterone (ng/dl)	547	17.6 (0.4)	413	79.7 (2.7)	288	74.8 (3.6)
DHT (ng/dl)	271	7.65 (0.34)	143	20.98 (0.98)	169	21.04 (0.97)
SHBG (nmol/l)	547	91.7 (2.5)	415	93.9 (2.8)	290	90.0 (3.6)

DHT = dihydrotestosterone, SHBG = sex hormone binding globulin
SEM = Standard Error of the Mean

Distribution:

In women, circulating testosterone is primarily bound in the serum to SHBG (65-80 %) and to albumin (20-30 %) leaving only about 0.5-2 % as the free fraction. The affinity of binding to serum SHBG is

relatively high and the SHBG bound fraction is regarded as not contributing to biological activity. Binding to albumin is of relatively low affinity and is reversible. The albumin-bound fraction and the unbound fraction are collectively termed 'bioavailable' testosterone. The amount of SHBG and albumin in serum and the total testosterone concentration determine the distribution of free and bioavailable testosterone. Serum concentration of SHBG is influenced by the route of administration of concomitant estrogen therapy.

Metabolism:

Testosterone is metabolised primarily in the liver. Testosterone is metabolised to various 17-ketosteroids and further metabolism results in inactive glucuronides and other conjugates. The active metabolites of testosterone are estradiol and dihydrotestosterone (DHT). DHT has a greater affinity to SHBG than does testosterone. DHT concentrations increased in parallel with testosterone concentrations during Intrinsa treatment. There were no significant differences in serum estradiol and estrone levels in patients treated with Intrinsa for up to 52 weeks compared to baseline.

On removal of an Intrinsa patch, testosterone serum concentrations return to near baseline values within 12 hours due to its short terminal exponential half-life (approximately 2 hours). There was no evidence of accumulation of testosterone over 52 weeks of treatment.

Elimination:

Testosterone is mainly excreted in the urine as glucuronic and sulphuric acid conjugates of testosterone and its metabolites.

5.3 Preclinical safety data

Toxicological studies of testosterone have only revealed effects which can be explained based on the hormone profile.

Testosterone has been found to be nongenotoxic. Non-clinical studies on a relationship between testosterone treatment and cancer suggest that high doses may promote tumour growth in sex organs, mammary glands and liver in laboratory animals. The significance of these data for the use of Intrinsa in patients is not known.

Testosterone has a masculinising effect on female rat foetuses when dosed subcutaneously at 0.5 or 1 mg/day (as the propionate ester) to pregnant rats during organogenesis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing layer:

Translucent polyethylene backing film printed with proprietary ink containing sunset yellow FCF (E110), latolrubine BK (E180) and copper phthalocyanine blue pigment.

Self adhesive matrix drug layer:

Sorbitan oleate,
Acrylic co-polymer adhesive containing 2-Ethylhexylacrylate – 1-Vinyl-2-pyrrolidone co-polymer.

Protective release liner:

Siliconised polyester film.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

Do not refrigerate or freeze.

6.5 Nature and contents of container

Each patch is packed in a sealed laminated sachet. The sachet material comprises of food grade paper/polyethylene/aluminium foil/ethylene methacrylic acid copolymer (outer to inner layer). The ethylene methacrylic acid copolymer (Surlyn[®]) is the heat seal layer which allows the two laminate sachet stocks to be heat-sealed together to form the sachet.

Cartons of 2, 8 and 24 patches.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Procter & Gamble Pharmaceuticals UK Ltd.
Rusham Park Technical Centre
Whitehall Lane
Egham
Surrey
TW20 9NW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT